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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,157	07/12/2002	Takashi Saito	NAII 118755	9352

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT PAPER NUMBER

1635

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/070,157	Applicant(s) SAITO, TAKASHI	
	Examiner Richard Schnizer, Ph. D	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 32,34,37-44,46,49-56,58,61-70,73-80 and 83-97 is/are pending in the application.
- 4a) Of the above claim(s) 84-97 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32,34,37-44,46,49-56,58,61-70,73-80 and 83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

An amendment was received and entered on 11/30/05.

Claims 33, 35, 36, 45, 47, 48, 57, 59, 60, 71, 72, 81, and 82 were canceled as requested.

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83-97 remain pending.

Claims 84-97 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/25/05.

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83 are under consideration in this Office Action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 9/09/1999 (11-255024). It is noted, however, that applicant has not filed a certified copy of the Japanese application as required by 35 U.S.C. 119(b).

Rejections Withdrawn

Applicant's amendments overcame the previous rejections under 35 USC 112, second paragraph of claims 32, 34, 37-44, 46, 49-56, 58, 61-70, and 73-80, but necessitated new indefiniteness rejections as discussed below.

Applicant's amendments overcame the previous grounds of rejection under 35 USC 112, first paragraph for lack of written description and enablement, but necessitated new rejections for introduction of new matter and lack of enablement, as set forth below.

Applicant's amendments overcame the previous rejections under 35 USC 102 and 103, necessitating new rejections under 35 USC 103. See below.

The double patenting rejection of claims 56-60 and 79 over US 6,753,171 is overcome by Applicant's statement on the record at page 14 of the response that the conflicting inventions were commonly owned at the time the instant invention was made. See 37 CFR 1.78(c).

Claim Objections

Applicant's amendments overcame the previous claim objections.

Claims 32, 37-39, 42-44, 49-51, 54, 56, 61-63, 67-70, 73-75, 78-80, and 83 are objected to because they have incorrect status identifiers. These claims are currently identified as "Withdrawn" or "Withdrawn-currently amended". In fact although these claims are linking claims, none of them is withdrawn, all are under consideration, and so all should be identified as either "original" or "currently amended". Applicant is required to use the proper status identifiers pursuant to 37 CFR 1.121.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32, 34, 37-44, 46, 49-56, 58, 61-70, 73-80, and 83 are indefinite because it is unclear what is meant by "perforation of the membrane recovers to the state prior to perforation". Does Applicant mean that the membrane recovers to its state prior to perforation? How can "perforation recover"?

Claim 53 is indefinite. It appears that Applicant may have inadvertently deleted the word "said" immediately after "wherein". The result is a claim that requires light that has been transmitted through the side wall of a capillary to be applied to said denaturing substance from the tip of said capillary. However, if the light has been transmitted through the side wall of the capillary, it cannot be applied to the denaturing substance from the tip of the capillary unless the light is first redirected back into the capillary. The claim is incomplete because it lacks these essential steps. This rejection can be overcome by reinserting the word "said" immediately after "wherein". See e.g. claim 52.

Claim 65 is indefinite because it is ungrammatical. It appears Applicant inadvertently deleted the words "wherein said".

Claims 73 and 83 are indefinite because they recite "the capillary" without antecedent basis.

Response to Arguments

Applicant's arguments filed 11/30/05 have been fully considered to the extent that they reply to the rejections above but they are not persuasive.

Applicant asserts at page 12 of the response that claim 83 was cancelled. However, claim 83 is listed in the claims as (Withdrawn-currently amended), and cancellation of claim 83 was not directed at any point in Applicant's response. As a result it is considered to be pending and remains under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 70, 75, and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 70, 75, and 80 have been amended to require permeabilization of a membrane by the method of claim 32, 44, or 56, i.e. by bringing a photosensitizer or photocatalyst into contact or close proximity with the membrane and providing stimulatory light for the photosensitizer or photocatalyst. Claims 70, 75, and 80 further recite "injecting a desired substance inside the membrane." There are two ways to

interpret these claims. In the first, the “injecting a desired substance inside the membrane” step could be considered to be an unnecessary recitation of a step already carried out in the method of claim 32, 44, or 56. In this interpretation, claims 70, 75, and 80 fail to further limit claim claims 32, 44, or 56. As a result, these claims are interpreted instead as requiring a second, separate administration of a photosensitizer or photocatalyst into contact with a membrane. The specification as filed does not appear to support such a method, and Applicant did not point to any support in the specification for the claims as amended. As set forth in MPEP 2163.06:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not “new matter” is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

Absent support in the specification, the claims as amended introduce new matter into the disclosure.

Scope of Enablement

Claim 73, 78, and 83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods as claimed wherein a capillary is caused to penetrate a cell membrane or artificial membrane, does not reasonably provide enablement for such methods in which a capillary is made to penetrate an intracellular membrane. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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The claims as amended embrace an embodiment in which a capillary is used to penetrate an intracellular membrane for injection of a substance into the membrane.

The prior art of record (Bataille et al (J. Cell. Biol. 111: 1571-1582, 1990) and Laffafian et al (Biophys. J. 75:2558-2563, 1998) taught methods of penetrating cell membranes with capillary micropipettes. The prior art of record offers no example of penetrating an intracellular membrane such as a lysosome, endosome, mitochondrion, endoplasmic reticulum, or nuclear membrane, with a capillary as required by the instant claims.

The instant specification offers no working example of such a procedure, nor any guidance as to how to produce a capillary small enough and stable enough to penetrate an intracellular membrane for the purpose of injecting a molecule into the membrane.

While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In *Genentech, Inc, v Novo Nordisk A/S*, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, how to make and use a capillary small enough and stable enough to penetrate an intracellular membrane for the purpose of injecting a molecule into the membrane is not a minor detail that can be overlooked in the process of providing an enabling disclosure. Instead it is a critical element of the invention that is not disclosed. In view of the state of the art and the lack of guidance and examples in the specification one of skill in the art would have to perform undue experimentation in order to practice the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 32, 34, 37-39, 44, 46, 49-51, 56, 58, 61-63, 66, 69, 70, 74, 75, 79, and 80 rejected under 35 U.S.C. 103(a) as being unpatentable over Berg et al (WO 96/07432), in view of Chen et al (US Patent 5,445,608).

Berg taught methods of delivering molecules to the cytosol of cells by delivering the molecule and a photosensitizer/photocatalyst to a cell, allowing cellular uptake of the molecule and photosensitizer in to the endosomal/lysosomal pathway, excitation of the photosensitizer with light of the appropriate wavelength, and release of the molecule from the endosome or lysosome, or other cellular compartment, without loss of cellular

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function. See paragraphs bridging pages 2-3 and 5-6. Contemplated photosensitizers included ALPcS_{2a}, which requires UV light for excitation. See e.g. page 10, lines 3-14. Although Berg did not explicitly teach recovery of perforated membranes, it would have been obvious to one of ordinary skill in the art at the time of the invention to adjust the concentration of photosensitizer, and/or the intensity or duration of light exposure, such that membrane damage was reversible in view of the stated objective of not losing cellular function.

Berg did not teach a membrane-destroying member, a supporting member that brings a photosensitizer and carries light from a light source, or a stimulus carrying member that locally introduces the light to a site in the membrane.

Chen taught methods of photodynamic therapy (PDT) by delivery of a photoreactive agent to a cell and illumination of the cell with stimulatory light. See abstract; column 1, lines 15-36; column 4, lines 3-16, column 5, lines 9-15 and column 7, lines 6-12. In particular, Chen taught that the method could be practiced with the apparatus shown in Fig. 17 which allows one to deliver a photosensitizer through a catheter which also comprises an optical fiber. This arrangement allows precise illumination at the site of photosensitizer delivery. See column 23, line 42 to column 24, line 9; and column 24, lines 16-31. The catheter functions as the instantly recited capillary, and the optical fiber functions as the membrane destroying member, supporting member, and stimulus carrying member of the instant claims.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the apparatus of Chen in the method of Berg because the apparatus of

Chen allows precise illumination at the site of photosensitizer delivery. See column 23, line 42 to column 24, line 9; and column 24, lines 16-31.

The photosensitizers of Berg and Chen are considered to be photocatalysts for the reasons of record at page 16 of the Action mailed 7/28/05, i.e. because they function by first being excited by light into an energized state, then transferring that energy to molecular oxygen to produce singlet oxygen, and to thereby return to the ground state and regenerate the photocatalyst.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 11/30/05 have been fully considered but they do not apply to the new ground of rejection set forth above. Applicant's objection to the reliance on Hale and Morgan for supporting evidence (in the now withdrawn 102 rejection) appears unfounded. Hale provided evidence that the photosensitizers of Chen inherently accumulate in membranes, and Morgan provided evidence that the photosensitizers of Chen function as catalysts, as discussed at page 16 of the Action mailed 7/28/05.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

A handwritten signature in black ink, appearing to read 'Richard Schnizer', with a long horizontal flourish extending to the right.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635